REMARKS

Applicants hereby disclaim the priority of the earlier filed application 08/971,439 filed 17 November 1997, now patent No. 6,103,501; with the election of the present invention, benefit of this priority is not required.

The title has been changed to be more descriptive as requested by the Office. Claim 1 has been amended to limit it to the elected invention; the added limitation that if β^1 is CG, then β^2 is not FSH is supported by the same provision that already occurs in claims 11 and 12. Claim 2 has been amended for clarity as also requested by the Office. New claims 21-28 simply specify the alternative possibilities inherent in the description of β^1 and β^2. No new matter has been added and entry of the amendment is respectfully requested.

Applicants indicated in their response to an initial restriction requirement, along with the species election, that claims 1-2, 5-6, and 10-12 read on the elected species which was that wherein both β^1 and β^2 confer FSH agonist activity. The Examiner has correctly noted that claim 3 falls within the scope of the elected species. Applicants concur, and also note that apparently claim 9 should have been listed by them since claim 10, dependent thereon, includes the elected species. It appears that the Office has graciously examined the considered claims with respect to species in addition to that elected – the art citations relate to combinations of FSHβ and LHβ or FSHβ and hCGβ. Accordingly, it is believed that all of claims 1-12 may properly be considered.

<u>The Rejection Under 35 U.S.C. § 112, First Paragraph</u>

All considered claims were rejected under 35 U.S.C. § 112, first paragraph, on the basis of scope. There were two aspects of this rejection, which are addressed separately below.

First, it was asserted that the specification was enabling for compositions in which β^1 and β^2 were from the same vertebrate species, but not for instances wherein different species were

represented by the β^1 and β^2 subunits. Presumably the same logic would apply to the α subunit. This, however, assumes a limitation that is not set forth in the claims. The claims do not require that the β^1 and β^2 subunits be derived from different species.

If, as the Office asserts, it is generally known that it would be disadvantageous to administer compositions where the various subunits are derived from different species, then one of ordinary skill simply would not do that. If this is a foregone conclusion, it need not be stated in the claim. For example, it is not necessary in this claim to further state that the administering would not include ways of administering proteins that are clearly ineffective, such as in the form of an oral potion.

If, on the other hand, the proposition noted by the Office is not generally known (*i.e.*, that one would not choose subunits from different vertebrate species, or would make some subset of choices), then the Office must provide some evidence that this choice is inoperable. Respectfully, insufficient documentation and reasoning has been provided in support of this rejection.

It thus appears, as between these alternatives, that the Office is asserting that it is generally known that it is preferred to provide all of the subunits as derived from the same species and does not believe that further substantiation is necessary. If so, there is no need to state this in the claim.

The second basis for this rejection is that when the two β subunits are from the same glycoprotein hormone, the specification does not enable the use of the invention because:

> It is not predictable that a single chain complex of a single chain $\alpha\beta$ fusion with a noncovalently linked β subunit can demonstrate both activities simultaneously, and scientific reasoning would not lead to the conclusion that it can.

Again, it appears that the Office is reading into the claims a limitation that is not there. There is no requirement in the claim that the activities be exhibited simultaneously or that the FSH activities of the compounds of formulas (1) or (2) be greater than the agonistic activities of a particular compound with a single β subunit. The section quoted on page 4 merely states that this complex would have a greater activity during the circulating halflife of the complex than it would after one of the FSHβ subunits disappears. This is not, however, a claim requirement.

In addition, there is no evidence that an α subunit coupled to a β subunit in a single chain configuration is unable to associate with an additional β subunit. The evidence in the specification is to the contrary; Example 4 establishes that such a complex was formed and assessed by immunoprecipitation on SDS gels, in addition to testing for activities both of FSH and CG. The two papers cited by the Office, Lapthorn, *et al.*, *Nature*, 369:455 and Patel, *Nature*, 369:438 describe the crystal structure not of the single chain form of the hormone (βα or αβ) but of the heterodimer. There is no evidence of record that the single chain form and the heterodimer have identical crystal structures. So the disclosure of these papers is irrelevant.

The theory proposed by the Office appears to be that the reason applicants were able to demonstrate both CG and FSH activities in Example 4 is that there must have been some kind of dynamic equilibrium whereby at one point one β subunit was associated and at another, the other was associated. But there is no support for this theory. And it is unlikely. The β subunit of FSH is already coupled to the α subunit in Example 4. There is no way it can be detached. If the Office has the theory that the single chain form flips open and closed at some specified frequency so as to admit and then preclude binding of the alternate, noncovalently associated β submit, no evidence is offered to support this hypothesis. Accordingly, there is no basis for doubting the statements made in the specification that the dual function composition composed of a covalently linked α and β subunit and a noncovalently associated β subunit is workable to

exhibit both functions. This is true even if, as suggested by the Office, similar functions are provided by both β subunits. As noted, one β subunit may have a longer half-life than the other, or one may simply be more potent than the other.

For the reasons stated above, the rejection under 35 U.S.C. § 112, first paragraph, may properly be withdrawn.

The Rejections Over the Art.

First, applicants note that the embodiment wherein β^1 is CG and β^2 is FSH has been excluded from all claims. Thus, the glycoprotein hormone described by Hyde, *et al.*, has been excluded from the claims. Applicants further point out that the cited abstract by Ben-Menahem, *et al.*, is published within one year prior the application date herein, and is the work of the same inventors. The additional co-authors of this abstract, Hyde, Pixley, Perlan, and Hsueh, either worked under the direction of the inventors herein, or simply performed assays on their behalf. If necessary, a *Katz* declaration can be provided, although applicants are certain that the Examiner is aware that mere co-authorship does not raise the presumption of co-invention *In re Katz*, 687 F2d 450, 215 USPQ 14 (CCPA 1982).

Claims 1-3, 5 and 6 were rejected as obvious over Seethalakshmi, *et al.*, in view of both Hyde and Ben-Menahem, *et al.* As Hyde and Ben-Menahem are cited together, it is assumed that this basis for rejection requires the application of both secondary references. As Ben-Menahem has been removed as a citable document, this basis for rejection must fall on that basis alone. It is further noted that claims 10-12 are not included in this rejection and are therefore assumed free of the cited art.

The Office asserts that it would have been obvious to the person of ordinary skill to substitute, for the combination of hCG and FSH taught in the method of Seethalakshmi, the "hCGβα plus FSHβ" complex taught by Hyde or the "FSHβα plus hCGβ" complex as taught by

Ben-Menahem, *et al.* However, the composition taught from Hyde is excluded from the claims, and the composition taught by Ben-Menahem is not prior art to the present applicants. Accordingly, the claims are free of this rejection.

Claims 1-3, 5, 6 and 11-12 were rejected as obvious over De Rosa, *et al.*, in combination with the same Hyde and Ben-Menahem documents. It is unclear why claims 11 and 12 are considered unpatentable in the context of this rejection, but not in the previous one; it is further noted that claim 10 is free of this rejection also and has not been rejected over the art.

De Rosa is cited as administering the combination of FSH and LH assertedly for the treatment of fertility.

Again, applicants note that Hyde and Ben-Menahem are not cited in the alternative, but as a combination. The removal of Ben-Menahem as prior art thus defeats this rejection.

In any event, there is no suggestion in Hyde (or Ben-Menahem) to provide a composition containing the complex of FSHβα and LHβ or LHβα and FSHβ. A reading of Hyde confirms that it is entirely concerned with complexes of hCGβα and FSHβ. No alternative constructions are suggested at all. Conversely, Ben-Menahem addresses only FSHβα and hCGβ and suggests no alternative compositions. There is nothing to suggest to the skilled artisan that the teachings of Hyde (the only citable secondary reference) with De Rosa.*

Assuming, *arguendo*, that hMG contains FSH and LH, it is definitely a stretch to say that this administration to children with undescended testes is a treatment for infertility. This is not the common understanding of infertility treatments and certainly not the type of treatment envisioned by applicants in regard to claim 5. Accordingly, claims 5 and 6 are clearly free of this rejection.

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* Applicants assume that hMG is indeed comprised of FSH and LH, although this evidence is not of record, and it is not apparent from the abstract itself. If it can be established that what was actually administered in De Rosa was a combination of FSH and LH, applicants believe that evidence for this should be made of record.

Taken at face value, applicants are unable to find anything in these documents, even when combined, that would suggest preparation of FSHβα ≈ LHβ complex or a LHβα ≈ FSHβ complex for any reason. This is not suggested by Hyde or by De Rosa alone or together.

It will be noted that the none of the criteria which would support motivation set forth in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) are met. The suggestion for combination is not found in either document; the documents are not designed to solve the same problem, nor does one document provide the solution for a problem noted in another. Certainly neither document is a high profile document that would be well known to all skilled artisans. Therefore, there is no motivation to make any combination of Hyde with De Rosa. As stated above, even when combined, clearly the subject matter of claims 5-6 is not suggested, nor is the subject matter of claims 11 and 12. Since it is not even clear from De Rosa that there is a combination of FSH and LH being administered and there is no suggestion in Hyde that any combination of these β subunits at all be made. Similar comments apply to claims 1-3. Accordingly, this basis for rejection may also be withdrawn.

CONCLUSION

The claims have been amended to read only on the elected invention. It is believed that all claims should be considered as the claims withdrawn from consideration were thus withdrawn by virtue of a species election, and it is evident from the art cited that the examination was not limited to the elected species. Applicants believe that they have shown that the claims are of appropriate scope; they are directed to embodiments which those of ordinary skill would recognize as workable without the necessity of explicitly excluding any embodiments that would automatically be assumed inappropriate. The evidence offered by the Office in support of the theory that the compositions do not function as described is not germane as that evidence does not pertain to the compositions at issue here, but rather to the combination of a heterodimer with

an additional β subunit. The rejections over the art may be withdrawn because one of the documents required in support of the rejection is the work of the present inventors within a year prior the application herein. In addition, there is no motivation to combine the documents cited, nor does the invention result when the documents are combined. It is noted that claim 10 is apparently free of any art rejection. Accordingly, applicants respectfully request that claims 1-12 and 21-28 be passed to issue herewith.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 295002005900.

Respectfully submitted,

Dated: September 4, 2002 By: Kate H. Murashige

Kate H. Murashige
Registration No. 29,959

Morrison & Foerster LLP
3811 Valley Centre Drive,
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5112
Facsimile: (858) 720-5125

EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Amended) A method to provide a subject with different glycoprotein hormone activities which method comprises administering to a subject in need of said activities a composition of the formula:

$[\beta^1\text{-(linker}^1)_m\text{-}\alpha\text{-(linker}^2)_n\text{-}\beta^2$ (1);

$\beta^1\text{-(linker}^1)_m\text{-}\beta^2\text{-(linker}^2)_n\text{-}\alpha$ (2);

$\alpha\text{-(linker}^1)_m\text{-}\beta^1\text{-(linker}^2)_n\text{-}\beta^2$ (3);]

$\beta^2 \approx \alpha\text{-(linker)}_m\text{-}\beta^1$ [(4)] (1); or

$\beta^1\text{-(linker)}_m\text{-}\alpha \approx \beta^2$ [(5)] (2)

wherein each of β^1 and β^2 has the amino acid sequence of the β subunit of a vertebrate glycoprotein hormone, or a variant thereof;

"α" has the amino acid sequence of the α subunit of a vertebrate glycoprotein hormone or a variant thereof;

"linker" is a linker moiety; and

"≈" is a noncovalent link between α and β^2;

[each of] m [and n] is [independently] 0 or 1;

wherein each of β^1 and β^2 confer a different activity on said composition,

with the proviso that if β^1 is CGβ then β^2 is not FSHβ.

2. (Amended) The method of claim 1 wherein β^1 and β^2 [correspond to different] are native β subunits.

6. (Amended) The method of claim 5 wherein

both β^1 and β^2 confer FSH agonist activity on said composition; or

[wherein] both β^1 and β^2 confer CG agonist activity; or

[wherein] both β^1 and β^2 confer LH antagonist activity; or

[wherein] one of β^1 and β^2 confers FSH agonist activity and the other confers LH antagonist activity or lowered LH agonist activity; or

[wherein] one of β^1 and β^2 confers FSH agonist activity and the other confers CG agonist activity; or

[wherein] one of β^1 and β^2 confers LH antagonist activity or lowered LH agonist activity and the other confers CG agonist activity.

10. (Amended) The method of claim 9 wherein

one of β^1 and β^2 confers FSH agonist activity and the other confers LH antagonist activity or lowered LH agonist activity on said composition; or

[wherein] both β^1 and β^2 confer FSH agonist activity; or

[wherein] both β^1 and β^2 confer LH antagonist activity.

11. (Amended) A glycosylated or nonglycosylated composition of the formula

$\beta^2 \approx \alpha\text{-(linker)}_m\text{-}\beta^1$ [(4)] (1); or

$\beta^1\text{-(linker)}_m\text{-}\alpha \approx \beta^2$ [(5)] (2)

wherein each of β^1 and β^2 has the amino acid sequence of the β subunit of a vertebrate glycoprotein hormone, or a variant thereof;

"α" has the amino acid sequence of the α subunit of a vertebrate glycoprotein hormone or a variant thereof;

"linker" is a linker moiety; and

"≈" is a noncovalent link between α and β^2;

m is 0 or 1;

wherein each of β^1 and β^2 confer a different activity on said composition; and

with the proviso that if β^1 is CGβ then β^2 is not FSHβ.

12. (Amended) A pharmaceutical composition which regulates the glycoprotein hormone concentrations in a mammal which comprises an effective amount of the composition of the formula

$\beta^2 \approx \alpha\text{-(linker)}_m\text{-}\beta^1$ [(4)] (1); or

$\beta^1\text{-(linker)}_m\text{-}\alpha \approx \beta^2$ [(5)] (2)

in admixture with at least one pharmaceutically acceptable excipient; and

wherein each of β^1 and β^2 has the amino acid sequence of the β subunit of a vertebrate glycoprotein hormone, or a variant thereof;

"α" has the amino acid sequence of the α subunit of a vertebrate glycoprotein hormone or a variant thereof;

"linker" is a linker moiety; and

"≈" is a noncovalent link between α and β^2;

each of m and n is independently 0 or 1;

wherein each of β^1 and β^2 confer a different activity on said composition; and

with the proviso that if β^1 is CGβ then β^2 is not FSHβ.